REMARKS

I. Preliminary Remarks

Claims 125, 127-130, 132, 148, 149, 155-159, and 213-261 are pending. All claims are subject to examination pursuant to the decision on petition dated August 22, 2007. All rejections in the Office Action mailed March 12, 2007 are mooted by cancellation of claims 204-212 herein.

Applicants note that corresponding claims to the p75 TNFR fusion proteins are currently under prosecution in U.S. Patent Application No. 08/444,790 (denoted herein as "the '790 Application"). The Examiner in the '790 Application rejected these claims under 35 U.S.C. §§ 103 and 112, first paragraph. The two most recent Office Actions, mailed April 3, 2006 and February 23, 2007, are attached hereto as Exhibits I and II.

Submitted herewith are complete copies of Applicants responses in the '790 Application (Exhibits III and IV), mailed October 3, 2006 and August 2, 2007, respectively, with exhibits and accompanying declarations, including: (a) the Third Declaration of Dr. Werner Lesslauer Under 37 C.F.R. § 1.132 (Exhibit V), (b) the Declaration Under 37 C.F.R. § 1.132 of Stewart Lyman, Ph.D. (Exhibit VI), and (c) the Second Declaration of Stewart Lyman, Ph.D. Under 37 C.F.R. § 1.132 (Exhibit VII). For completeness of the record, Applicants also submit herewith the Declaration [II] of Dr. Werner Lesslauer Under 37 C.F.R. §1.132 (Exhibit VIII), originally filed in parent application U.S. Ser. No. 08/095,640. An Information Disclosure Statement containing a 1449 form listing the references referred to in these responses and declarations will be filed in the near future.

Applicants respectfully request that the Examiner in the present application consider the evidence submitted in the '790 Application in examining the present claims directed to polynucleotides encoding p75 TNFR fusion proteins, vectors, host cells, and methods of using such polynucleotides to produce protein.

During prosecution in the '790 Application, Applicants argued that the cited art teaches away from combining Dembic with Capon, and that there was no reasonable expectation of success in producing the TNF-binding fusion proteins encoded by the claimed

polynucleotides because of the uncertainties associated with the trimeric structure of TNF and the unknown spatial geometry of the binding interaction between TNF and TNFR. Thus, there is no *prima facie* case of obviousness.

In addition, during prosecution in the '790 Application, Applicants argued that there are a multitude of unexpected results that rendered p75 TNFR fusion proteins nonobvious. The fusion proteins exhibit different types of properties that would not have been predicted based on the behavior of other immunoglobulin fusion proteins in the prior art. The first category of unexpected results relates to the unique binding stoichiometry of the dimeric TNF-binding fusion proteins with trimeric TNF, and the corresponding lack of ability to form aggregated protein complexes. The second category of unexpected results relates to the surprising and marked reduction in immunoglobulin effector functions of the fusion proteins encoded by the claimed polynucleotides. The third category of unexpected results relates to the improved binding kinetics (both affinity and kinetic stability) and potency in *in vitro* biological activity assays.

Where the prior art would have predicted the presence of an activity, the absence or significant reduction of that activity is a novel and unexpected property proving nonobviousness. Similarly, where the prior art would have predicted no improvement in an activity, an improvement in activity constitutes a novel and unexpected property. In particular, the improvement in potency (100-fold in some cases) is so marked that it may be classified as a different property entirely. A marked improvement may be "classified as a difference in kind [of property], rather than one of degree." See *In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974).

II. Support for Amendments

A. Amendments to the specification to insert material from Smith (1990)

The material being inserted into the specification in the paragraphs beginning at page 4, line 36 and page 10, line 1 is the same material previously incorporated by reference at page 10, line 10 and thus the amendment does not add new matter. Applicants

have amended the specification and sequence listing to insert the sequence of the TNF receptor protein described in Smith et al., Science 248, 1019-1023, (1990) ("Smith (1990)") as SEQ ID NO: 27, and to insert text from Smith (1990) that describes that sequence. Smith (1990) describes the cloning of cDNA encoding the p75 TNF receptor, characterization of the nucleotide and amino acid sequences, and characterization of the properties of the encoded TNF receptor protein.

The sequence of the TNF receptor protein described in Smith (1990) was clearly intended to be incorporated as part of Applicants' invention, as evidenced by the statements at page 9, line 19 through page 10, line 10 of the specification:

> [T]he present invention is also concerned with DNA sequences coding for proteins and soluble or non-soluble fragments thereof, which bind TNF.
>
> * * *
>
> That is to say, the present invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4, whereby ***in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP. One sequence which results from such a deletion is described***, for example, in [Smith et al.,] Science *248*, 1019-1023, (1990). [Emphasis added.]

This quote makes clear that Applicants intended their invention to embrace the p75 TNF receptor DNA sequences, and the proteins coded thereby, that are disclosed in Smith (1990). The journal name, volume number, page numbers, and year of the Smith article are set forth at page 10, line 10 and uniquely identify this publication. Figure 3B of Smith (1990) displays a full-length deduced amino acid sequence of p75 TNF receptor. The legend to Figure 3B provides the Genbank accession number associated with the deposit of the nucleotide sequence. The legend to Figure 3B also describes the markings in the figure that show the leader region (i.e., the signal sequence which is cleaved to form the mature protein), the transmembrane domain, and potential N-linked glycosylation sites within the displayed amino acid sequence.

This inserted text from the legend of Figure 3B of Smith (1990) (the leader region is singly underlined, the transmembrane domain is shown boxed, and potential N-linked glycosylation sites are doubly underlined) exactly mirrors the information provided for the p55 sequence in Figure 1 of Applicants' specification (in which the leader region is indicated by negative numbers, the transmembrane region is underlined and the hypothetical glycosylation sites are identified by asterisks). See Fig. 1 and Brief Description of the Figures at page 4, lines 17-21 of the specification.

Applicants have amended their application at page 4, line 36 and at the paragraph beginning at page 10, line 1, by inserting the TNF receptor sequence described in Figure 3B of Smith (1990) as new Figure 5 (and as SEQ ID NO: 27), and inserting text from the legend of Figure 3B of Smith (1990) that describes the sequence. Applicants have also amended the paragraph at page 10, line 1 to be more closely consistent with the language recommended in the rules by inserting the language "incorporated by reference herein" after the citation of Smith (1990). Finally, Applicants have inserted a reference to the authors (Smith et al.) of the publication, although the authors' names are not necessary to identify the publication.

It is not new matter to insert information from a document that is identified and specifically referred to for that information in the application as filed. *See, e.g., In re Hawkins*, 486 F.2d 569, 575 (CCPA 1973). See also prior versions of MPEP §608.01(p) and current 37 CFR § 1.57 (f), (g). 37 C.F.R. §1.57(f) permits amendment of the specification to insert material incorporated by reference and 37 C.F.R. §1.57(g) permits the correction of a noncompliant incorporation by reference. Under 37 C.F.R. §1.57(g)(1) and (2), it is entirely proper to incorporate material where the application clearly conveys an intent to incorporate the material by reference and the material was sufficiently described to uniquely identify the document. Such is the case here.

B. Amendment to the specification to insert reference to deposit

The amendments to the specification in the paragraph beginning at page 10, line 11 insert deposit information relating to a DNA sequence described in the specification as originally filed. Submitted herewith is a Third Declaration of Dr. Werner Lesslauer Under

37 C.F.R. § 1.132 (Exhibit A, originally submitted in related application U.S. Ser. No. 08/444,790) confirming that the deposited DNA construct (deposited with the ATCC under accession no. PTA-7942) is the DNA sequence identified in the specification at page 10, line 11, that it was created before the effective U.S. filing date of the present application, and that the deposited DNA construct includes DNA encoding soluble portions of human p75 tumor necrosis factor receptor (TNFR). Insertion of the deposit accession number, the deposit date, and the name and address of the depository is not new matter because the deposited DNA was described in the specification as filed. See *In re Lundak* 773 F.2d 1216 (Fed. Circ. 1985).

Applicants also submit herewith a Budapest Declaration with respect to PTA-7942.

C. Amendments to the claims

The partial amino acid sequences of the p75 TNF receptor (e.g., SEQ ID NOS: 8, 9, 10, 12, 13) are found, e.g., at page 7, line 32 through page 8, line 12.

The recitation of p75 TNF receptor nucleic acid sequence obtainable from an HL-60 cDNA library and comprising the partial amino acid sequences identified at page 7, line 32 through page 8, line 12 of the specification finds support throughout the specification. For example, Applicants contemplated obtaining nucleic acid sequences from an HL-60 cDNA library, e.g., at page 12, lines 23-33, page 21, line 26 through page 23, line 2, and page 35, lines 22-36.

Support for the recitation in some claims of the p75 TNF receptor sequence of a cDNA insert of plasmid PTA-7942 deposited with the American Tissue Culture Collection (ATCC) is found, e.g., in the amended text at page 10, line 11 of the specification.

Support for the recitation in some claims of SEQ ID NO: 27 is found, e.g., in the amended text at page 10, line 1 of the specification.

Support for the recitation in some claims of "extracellular region" is found throughout the specification. The "extracellular part" and "extracellular region" of a TNF binding protein are disclosed in the examples, *e.g.*, at page 37, lines 15-18 ("extracellular

part"), page 42, lines 5-7 ("extracellular region"), which use the 55 kD TNF binding protein as the exemplary TNF binding protein. The Applicants disclose, at almost every instance, that the exemplary embodiments relate to both of the 55 kD and 75 kD TNF binding proteins that are the subject of the application. See, e.g., page 9, line 19 through page 10, line 10 and page 14, lines 32-36. The examples elsewhere teach that p75 TNFR is identified by ("[e]ssentially analogous techniques") to those used for p55 TNFR (see, *e.g.* page 35, lines 22-23). The use of the phrases "extracellular part" and "extracellular region" are thus equally applicable to either the 55 kD or the 75 kD TNF receptor. In fact, Applicants specifically state that the examples are illustrative and that these examples should not limit the scope of the invention. See page 20, lines 27-30. Accordingly, the ordinarily skilled artisan in the field is fully notified by the specification, as filed, that embodiments of the invention include the extracellular region of the 75 kD human TNF receptor.

As supplemental support, see the accompanying Declaration Under 37 C.F.R. § 1.132 of Stewart Lyman, Ph.D., particularly paragraphs 10-17 and 24. Dr. Lyman's conclusion upon reviewing the specification, including these cited portions, is that "one skilled in the art at the time would have understood that the application contemplated that the entire extracellular region of p75 TNFR was a specific example of a soluble fragment of a TNF binding protein." Paragraph 24 of the Declaration. Thus, the proposed amendment is fully supported by the application.

Other new claims parallel existing claims. IgG subtypes are disclosed, e.g., at page 11, line 10. Vectors, host cells and production methods are supported throughout the specification, e.g. at page 4, lines 7-13, page 12, lines 1-8 and page 15, line 1 to page 19, line 20.

D. Amendments to the sequence listing

The substitute sequence listing submitted herewith (a) adds reference to priority application European Patent Application No. 90116707.2 (certified copy previously submitted with response mailed February 15, 2006), (b) corrects a typographical error in the amino acid sequence set out as SEQ ID NO: 5 (the amino acid at position 24 of SEQ ID NO: 5 should be a GLN (Q) rather than a GLU (E) as shown in the amino acid sequence

designated "IA" at page 7, lines 27-29 of the specification as originally filed), and (c) adds the TNF receptor protein sequence disclosed at page 10, lines 9-10 as being described in Smith et al. *Science* 248:1019-1023, (1990) as SEQ ID NO: 27.

The correction of SEQ ID NO: 5 is not new matter because the correct sequence for sequence IA (SEQ ID NO: 5) is set out at page 7, lines 27-29 of the specification as originally filed. The addition of the TNF receptor protein sequence from Smith et al. *Science* 248:1019-1023, (1990) as SEQ ID NO: 27 is also not new matter for the reasons discussed above in section II.A.

Thus, the substitute sequence listing does not add new matter to the application.

CONCLUSION

Applicants believe the claims are in condition for allowance and early notice thereof is solicited. If further discussions with the attorneys of record would expedite prosecution, the Examiner is respectfully requested to contact Li-Hsien Rin-Laures at the number indicated below.

Dated: August 30, 2007

Respectfully submitted,

By William K. Merkel

William K. Merkel
Registration No.: 40,725
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant